Synthesis of 4,4-difluoro-1H-pyrazole derivatives.

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Abstract: Fluorination of 3,5-diarylpyrazole substrates by Selectfluor™ in acetonitrile gave 4,4-difluoro-1H-pyrazoles in addition to 4-fluoropyrazole derivatives. The structure of this new class of fluorinated heterocycle was established by X-ray crystallography.

Key words: organofluorine; fluoroheterocycle; pyrazole; selective fluorination; fluoropyrazole.

4,4-Difluoro-1H-pyrazole systems, a new class of fluorinated heterocycle, were synthesised by reaction of the corresponding diaryl-pyrazole and electrophilic fluorinating agent Selectfluor™.

The importance of fluorine containing aromatic and heterocyclic motifs to the pharmaceutical and agrochemical industries continues to grow[1] because approximately 5-15% of the total number of drugs launched worldwide over the past 50 years bear fluorinated substituents.[2] For example, many 6-membered fluorinated heteroaromatic derivatives find applications in a wide variety of drugs and plant protection agents such as Xeloda (anti-cancer, Roche), Voriconazole (antifungal, Pfizer), Ancobon (antifungal, Valeant) and Diclosulam (herbicide, Dow Agroscience).[2]

Whilst there are many reported examples of the synthesis of commercially important fluorinated 6-membered aza-heterocyclic rings, processes for the preparation of related fluorinated 5-membered ring systems are relatively rare.[3] However, interest in fluoropyrazole derivatives has increased recently due to their potential use for treating diabetes,[4] inflammatory disease,[5] as gastric acid inhibitors[6] and as acaricides.[7] Consequently, protocols for the synthesis of a variety of selectively fluorinated pyrazoles have been reported using either fluorination or 'fluorinated building block' strategies. Fluoro-cyclocondensation reactions involving enamino ketones[8] and fluorocyanoketones,[9] gold catalysed aminofluorination of alkynes[10] and reaction of hydrazines with fluoro-β-dicarbonyl substrates[11] offer efficient routes to various functional fluoropyrazole derivatives. Adaptation of established fluorination methodology such as halogen exchange[12] or Balz-Schiemann processes[13] has had limited success for the synthesis of fluoropyrazoles from appropriately functionalised pyrazole substrates due to low total yields over several synthetic steps. Potentially, the most efficient methods for the synthesis of fluoropyrazole systems are aromatic substitution processes using electrophilic fluorinating agents. A few examples of the preparation of various fluoroaminopyrazole systems from the reaction of aminopyrazole precursors with NFSI or Selectfluor™ have been recorded[14] whilst several 4-fluoropyrazole derivatives have been prepared by reaction of Selectfluor™ with a range of *N*-arylpyrazole substrates.[15]

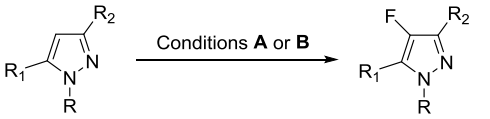
As part of a wider research programme concerning the synthesis of fluoroorganic systems using electrophilic fluorinating agents,[16] we were interested in broadening the scope of 'late-stage' fluorination reactions of pyrazole derivatives for applications in the life-sciences industries. In this paper, we describe electrophilic fluorination reactions of various pyrazole derivatives with either Selectfluor™ or fluorine gas which led to the unexpected synthesis of novel 4,4-difluoro-1H-pyrazole systems.

Pyrazole substrates **1** were either obtained from commercial suppliers or synthesised by reaction of the appropriate diketone derivatives with hydrazine or phenyl hydrazine by heating to reflux in ethanol following literature procedures.[17]

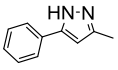
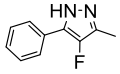
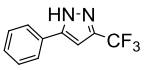
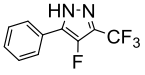
We began our pyrazole fluorination studies by investigating reactions of representative pyrazole systems **1a-c** with either Selectfluor™ or fluorine gas and the results are collated in Table 1. Reactions involving Selectfluor™ were carried out by heating the reaction mixture by using microwave irradiation (Conditions A). Fluorine gas, diluted to a 10% mixture (*v/v*) in dry nitrogen was passed at a controlled rate via a mass flow controller into a stirred solution of the substrate in acetonitrile using equipment discussed previously (Conditions B).[16] Mono-fluorinated pyrazoles **2a-c** were formed in modest yields and could be purified by column chromatography on silica gel. In contrast, fluorination of 3,5-dimethyl-1H-pyrazole was very inefficient due to extensive tar formation due to competing fluorination of the pendant methyl substituents and subsequent product degradation. In addition, pyrazole systems bearing two electron-withdrawing groups (CF_3, CO_2H, CO_2Me), gave no observed products upon reaction with either Selectfluor™ or fluorine gas, reflecting the lower nucleophilicity of these substrates, and starting materials were recovered in all of these reactions.

Monofluoro-pyrazole systems **2a-c** were identified by NMR and mass spectrometry techniques. In particular, the ^{19}F NMR spectra of these systems display singlet resonances at approximately -175 ppm, consistent with reported spectroscopic data reported for related fluoropyrazole systems.[15] In addition, the structure of **2b** was confirmed by X-ray crystallography (Fig. 1).[18]

Table 1 Synthesis of monofluoro-pyrazoles **2** using Selectfluor™ or fluorine gas.



Conditions **A**: Selectfluor™, 1 equiv., MW, 15 min, 90°C
Conditions **B**: 10% F_2/N_2, MeCN, rt

Pyrazole **1**	Conditions	Fluoropyrazole **2**
 **1a**	**A** **B**	 **2a**, 33 **2a**, 45
 **1b**	**A** **B**	 **2b**, 43 **2b**, 46*
 **1c**	**A** **B**	 **2c**, 43 **2c**, 40

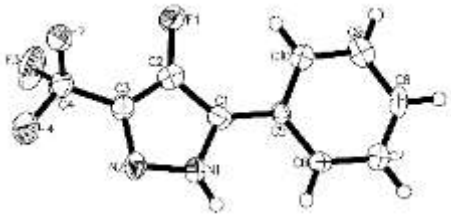
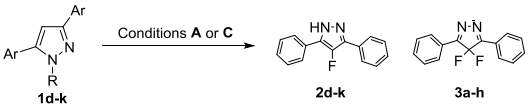


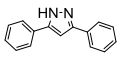
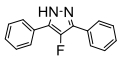
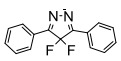
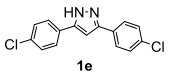
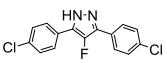
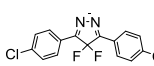
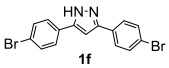
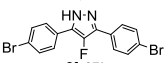
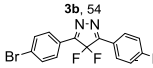
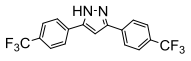
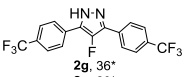
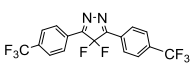
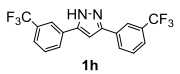
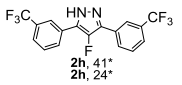
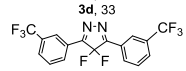
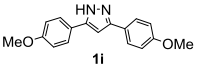
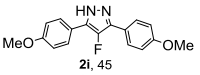
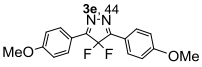
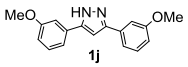
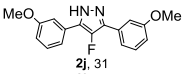
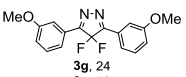
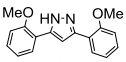
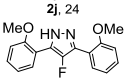
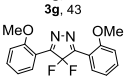
Figure 1 Molecular structure of **2b**

In order to expand the scope of the fluorination reactions we studied reactions of diphenylpyrazole substrates **1d-k** which unexpectedly gave mixtures of mono- and di- fluorinated systems **2d-k** and **3a-h** even when only one equivalent of Selectfluor™ was used and these results are collated in Table 2 (Conditions A). In all reactions, separation and purification of the difluorinated products **3a-h** were readily achieved because, in general, they eluted from the silica gel column much more rapidly than the starting material and mono-fluorinated pyrazole systems. Separation of fluoropyrazole products from the corresponding starting materials proved to be very difficult but could be achieved in several cases. Yields of the 4,4-difluoro-1H-pyrazole products **3a-h** were improved upon reaction of the pyrazole substrates with two equivalents of Selectfluor™. (Table 2, Conditions C).

Table 2 Synthesis of fluoropyrazole and 1H-difluoropyrazole derivatives



Conditions **A**: Selectfluor™, 1 equiv., MW, 15 min, 90°C
Conditions **C**: Selectfluor™, 2 equivs., MW, 15 min, 90°C

Pyrazole **1**	Conditions	Fluoropyrazole **2**	Difluoropyrazole **3**
 **1d**	A C	 **2d**, 45 **2d**, 23	 **3a**, 21 **3a**, 52
 **1e**	A C	 **2e**, 31* **2e**, 15*	 **3b**, 22 **3b**, 54
 **1f**	A C	 **2f**, 37* **2f**, 19*	 **3c**, 22 **3c**, 54
 **1g**	A C	 **2g**, 36* **2g**, 20*	 **3d**, 51 **3d**, 33
 **1h**	A C	 **2h**, 41* **2h**, 24*	 **3e**, 20 **3e**, 44
 **1i**	A C	 **2i**, 45 **2i**, 20	 **3f**, 27 **3f**, 45
 **1j**	A C	 **2j**, 31 **2j**, 24	 **3g**, 24 **3g**, 43
 **1k**	A C	 **2k**, 42 **2k**, 17	 **3h**, 23 **3h**, 49

*Products **2e-h** could not be separated from starting materials **1e-h** respectively by column chromatography and yields were estimated by 19F NMR in these cases only.

In contrast, when 3,5-diarylpyrazoles **1d-k** were reacted with fluorine gas, many fluorinated products were observed by ^{19}F NMR analysis of the crude product mixture and no products could be isolated and purified. In these reactions, competing fluorination of the aromatic ring substituents occurs as determined by the observation of many signals in the aromatic region (δ_F -140 -160 ppm) of the ^{19}F NMR spectra of the crude product mixture.

Difluorinated products **3a-h** were characterized by distinctive singlet resonances at approximately -115 ppm in their ^{19}F NMR spectra and the structure of **3f** was confirmed by X-ray crystallography (Fig. 2).[18] The difluorinated pyrazole systems **3** are a novel class of fluorinated compounds although corresponding dichlorinated systems have been reported and their use in Diels-Alder reactions has been explored.[19]

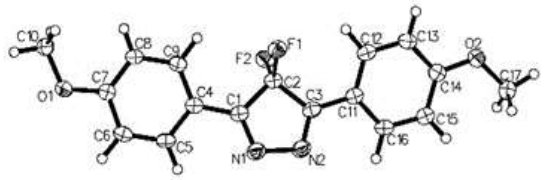
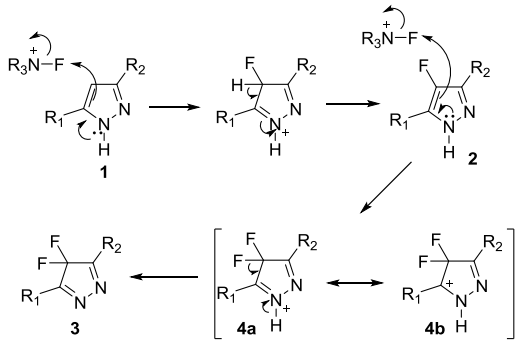


Figure 2 Molecular structure of **3f**

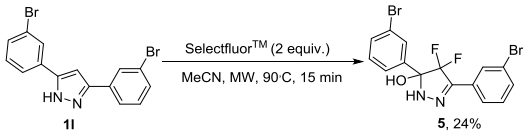
Initial fluorination of pyrrole derivatives occurs selectively at the 4-position consistent with an electrophilic aromatic substitution process (Scheme 1) and further electrophilic fluorination reaction occurs at the same site to give a difluorinated salt **4** as an intermediate. Deprotonation on work-up gives the observed 4,4-difluoro-1H pyrazole product **3**.



Scheme 1 Fluorination of pyrazole derivatives **2** and **3**

The intermediate carbocation **4b** is stabilized by the adjacent phenyl groups (R_1 = Aryl, Scheme 1) allowing difluorination to proceed as observed for 3,5-diarlpyrazole substrates.

In some cases a hydroxylated pyrazoline intermediate such as **5** was observed in crude product mixtures by ^{19}F NMR analysis and, for reaction with dibrominated system **1l**, the hydroxyl-pyrazoline **5** could be isolated albeit in low yield. This minor product is formed by reaction of water with intermediate salt **4** in reaction work-up, consistent with the mechanism shown in Scheme 1 and related reactions involving other halogenated 4H-pyrazoles.[20] The hydroxyl-pyrazoline product **5** could be identified by the presence of an AB system, with an appropriate J_{AB} 128 Hz coupling constant, in the ^{19}F NMR spectrum.



Scheme 2 Hydoxylated pyrazoline **5**

In conclusion, a method for the synthesis of unusual 4,4-difluoro-1H-pyrazole systems **3** has been established using shelf-stable, readily handled Selectfluor™ as the electrophilic fluorinating agent.

Experimental Section

Typical procedure (Conditions A)

4-Fluoro-3,5-diphenyl-1H-pyrazole ***2d*** *and 4,4-difluoro-3,5-diphenyl-4H-pyrazole* ***3a***

3,5-Diphenyl-1H-pyrazole (0.30 g, 1.36 mmol) and Selectfluor™ (0.482 g, 1.36 mmol) were dissolved in acetonitrile (5 mL) and the mixture heated by microwave irradiation for 15 minutes at 90 °C. The mixture was then extracted with DCM (3 x 50 mL) and washed with sodium bicarbonate (30 mL) and water (30 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel using hexane and ethyl acetate (1 : 1) as the eluent, gave *4-fluoro-3,5-diphenyl-1H-pyrazole* (0.135 g, 45 %) as pale yellow crystals; m.p. 185-188 °C (Found: $[MH]^+$, 239.0972. $C_{15}H_{11}FN_2$ requires: $[MH]^+$, 239.0983); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41-7.47 (2H, m, 4-H), 7.48-7.51 (4H, m, 3-H), 7.77-7.80 (4H, m, 2-H), 10.3 (1H, bs, NH); ^{13}C NMR (126 MHz; $CDCl_3$): δ 128.2 (Ar), 129.0 (Ar), 129.3 (Ar), 131.1 (d, $^2J_{CF}$ 15.0, C-3), 140.0 (d, $^1J_{CF}$ 226.6, C-4), 148.7 (Ar); ^{19}F NMR (376 MHz; $CDCl_3$): δ -174.3 (s); m/z (EI^+) 237.9 ($[M]^+$, 100 %), 107.8 (43), 76.9 (40); and, *4,4-difluoro-3,5-diphenyl-4H-pyrazole* **3a** (0.122 g, 21%) as yellow crystals; m.p. 105–107 °C; (Found $[MH]^+$, 257.0894. $C_{15}H_{10}F_2N_2$ requires: $[MH]^+$, 257.0890); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.67–7.44 (6H, m, Ar-H), 8.15–8.06 (4H, m, Ar-H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 125.4 (Ar), 125.6 (t, $^1J_{CF}$ 267.5, CF_2), 128.3 (Ar), 129.5 (Ar), 133.1 (Ar), 162.1 (t, $^2J_{CF}$ 23.1, C-2); ^{19}F NMR (376 MHz; $CDCl_3$): δ -116.3 (s); m/z (EI^+) 256.1 ($[M]^+$, 100 %), 153.0 (45), 103.1 (99), 77.1 (36).

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References

(1) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Purser, S.; Moore, P.R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (d) Muller, K.; Faeh, C.; Diedrich, F. *Science* **2007,** *317*, 1881-1886. (e) Ojima, I., (ed), *Fluorine in Medicinal Chemistry and Chemical Biology*. Wiley-Blackwell: Oxford, **2009**.

(2) (a) FY 2011 Innovative Drug Approvals. http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm. (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014,** *57,* 2832-2842.

(3) Petrov, V.A. *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry and Applications*, John Wiley and Sons, New York, 2009.

(4) Horiuchi, Y.; Nunami, N.; Tatamidani, H.; Ohata, E. PCT Intl. Appl. WO 2009020137 AI 20090212, 2009.

(5) Dressen, D.; Garofalo, A.W.; Hawkinson, J.; Hom, D.; Jagodzinski, J.; Marugg, J.L.; Neitzel, M.L.; Pleiss, M.A.; Szoke, B.; Tung, J.S.; Wone, D.W.G.; Wu, J.; Zhang, H. *J. Med. Chem.* **2007**, *50*, 5161.
(6) Large, M.S. Eur. Pat. Appl. EP 61318 A2 19820929, 1982.
(7) Ohata, S.; Kato, K.; Toriyabe, K.; Ito, Y.; Hamaguchi, R.; Nakano, Y. PCT Intl. Pat. Appl. WO 2009051245 AI 20090423, 2009.
(8) Surmont, R,; Verniest, G.; DeSchrijver, M.; Thuring, J.W.; ten Holte, P; Derouse, F.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 4105.
(9) Surmont, R.; Verniest, G.; De Kimpe, N. *Org. Lett.* **2010**, *12*, 4648.
(10) Qian, J.; Liu, Y.; Zhu, J.; Jiang, B.; Xu, Z. *Org. Lett.* **2011**, *13*, 4220.
(11) (a) Sloop, J.C.; Bumgardner, C.L.; Loehle, W.D. *J. Fluorine Chem.* **2002**, *118*, 135. (b) Breen, J. R.; Sandford, G.; Yufit, D. S.; Howard, J. A. K.; Fray, J.; Patel, B. *Beilstein J. Org. Chem.* **2011**, *7*, 1048.
(12) Katoch-Rouse, R.; Horti, A.G. *J. Labelled Compd. Radiopharm.* **2003**, *46*, 93.
(13) Fabra, F.; Vilarrasa, J. *J. Heterocycl. Chem.* **1978**, *15*, 1447.
(14) Bentley, J.; Biagetti, M.; Di Fabio, R.; Genski, T.; Guery, S.; Kopf, S.R.; Leslie, C.P.; Mazzali, A.; Meletto, S.; Pizzi, D.A.; Sabbatini, F.M.; Seri, C. PCT Intl. Pat. Appl. WO 2008092888 A1 20080807, 2008.
(15) Sloop, J.C.; Jackson, J.L; Schmidt, R.D. *Heteroat. Chem.* **2009**, *20*, 341.
(16) (a) Chambers, R.D.; Parsons, M.; Sandford, G.; Moilliet, J.S. *J. Chem. Soc., Perkin Trans 1* **2002**, 2190. (b) Sandford, G, *J. Fluorine Chem.* **2007**, *128*, 90. (c) McPake, C.B.; Sandford, G. *Org. Proc. Res. Dev.* **2012**, *16*, 844.
(17) Grandberg, I. I.; Kost, A. N. *Adv. Heterocycl. Chem.* **1966**, *6*, 347.
(18) X-ray crystallographic data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1016969-1016970.
(18) Adam, W.; Ammon, H.; Nau, W. M.; Peters, K. *J. Org. Chem.* **1994**, *59*, 7067.
(19) Hansen, J.; Kim, Y.; Griswold, L.; Hoelle, G.; Taylor, D.; D. Vietti *J. Org. Chem.* **1980**, *45*, 76.

4,4-Difluoro-1H-pyrazoles